DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

M3914N

July 6, 2000

CBER-00-025

WARNING LETTER

CERTIFIED MAIL - RETURN RECEIPT REQUESTED

Miles D. White
Chairman and Chief Executive Officer
Abbott Laboratories, Inc.
One Abbott Park Road
Abbott Park, IL 60064

Dear Mr. White:

The Food and Drug Administration (FDA) conducted an inspection of Abbott Laboratories, Inc. located at 14th Street and Sheridan Road, North Chicago, Illinois, between March 13 and 22, 2000. During the inspection, FDA investigators documented violations of Section 501(a)(2)(B) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) and deviations from the applicable standards and requirements of Subchapter C Parts 210 and 211, and Subchapter F Parts 600-680, Title 21, Code of Federal Regulations (21 CFR). The deviations noted on the Form FDA 483, Inspectional Observations, issued at the conclusion of the inspection include, but are not limited to, the following:

1. Failure to establish appropriate time limits for the completion of each phase of production to assure quality of the drug product [21 CFR 211.111], in that no processing hold time has been established between the manufacture of Hemin solution and the start of lyophilization for the manufacture of Panhematin.

2. Failure to establish appropriate procedures for the validation of a sterilization process to prevent microbiological contamination of product [21 CFR 211.113(b)], in that product specific sterilizing filter validation studies (bacterial challenge and extractables) have not been completed for Panhematin.

3. Failure to establish and follow control procedures to monitor the output and to validate the performance of those manufacturing processes that may be responsible for causing variability in the characteristics of in-process material and the drug product [21 CFR 211.110(a)], in that specifications for bulk Hemin have not been established for the total related compounds, acetic acid content, and total residue solvents tests.

4. Failure to inform the Food and Drug Administration about each change in the product, production process, quality controls, equipment, facilities, responsible personnel, or labeling, established in the approved license application [21 CFR 601.12]. For example, the following changes have not been submitted:

   a) Change in the site of pyrogen testing for the finished product Panhematin;

   b) Changes in the temperature range and reflux time of reactor [redacted] used in the manufacture of Hemin;

   c) The addition of a hot pre-coat sparkler in the manufacture of Hemin.

5. Failure to establish and follow procedures for the selection of sterility test samples for batches of finished product Panhematin, to ensure that the samples selected represent all stages of the filling operation [21 CFR 610.12(d)(2), 21 CFR 211.160(a)].

6. Failure to maintain and follow adequate written procedures describing the handling of all written and oral complaints regarding a drug product [21 CFR 211.198] in that lot numbers were not obtained for 12 of 13 reported adverse events relating to Panhematin, during the time period of 16 months prior to the inspection.

We acknowledge receipt of your written response dated April 6, 2000, which addresses the inspectional observations on the Form FDA 483 issued at the close of the inspection. We have reviewed the contents of your response. Corrective actions addressed in your letter may be referenced in your response to this letter, as appropriate; however, your response did not provide sufficient detail to fully assess the adequacy of the corrective actions. Our comments and requests for further information regarding corrective action are detailed below. The items correspond to the observations listed on the Form FDA 483:

Item 1:
Please provide time frames for the completion of concurrent validation regarding maximum process times.

Item 5:
In your response you state that the change in the site of pyrogen testing for Panhematin will be included in Abbott's Annual Report. It is our view that this change should be reported as a Changes Being Effected in 30 Days supplement in accordance with 21 CFR 601.12 (c)(2)(i).

Item 8:
Please note that all training provided to employees should be documented.

Neither this letter nor the list of inspectional observations (Form FDA 483) is meant to be an all-inclusive list of deficiencies that may exist at your facility. It is your responsibility as management to assure that your establishment is in compliance with all requirements of the federal regulations. Federal agencies are advised of the issuance of all Warning Letters about drugs so that they may take this information into account when considering the award of contracts.

Please notify this office in writing within 15 working days of receipt of this letter, of any steps you have taken or will take to correct the noted violations and to prevent their recurrence. If corrective actions cannot be completed within 15 working days, state the reason for the delay and the time within which the corrections will be completed. Failure to promptly correct these deviations may result in regulatory action without further notice. Such actions include license suspension, revocation, and seizure. Your reply should be sent to the U.S. Food and Drug Administration, Center for Biologics Evaluation and Research, 1401 Rockville Pike, Suite 200 N, Rockville, Maryland 20852-1448, Attention: Division of Case Management, HFM-610. If you have any questions regarding this letter, please contact Ms. Mary Malarkey, Acting Director, Division of Case Management, at (301) 827-6201.

Sincerely,

Deborah D. Ralston
Director
Office of Regional Operations